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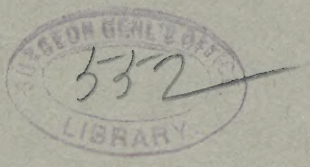


FROM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOL. I, NO. 1, 1896

# ON THE ACTION OF PIPERIDINE AND SOME OF ITS COMPOUNDS.

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In the course of a research undertaken for another purpose I had occasion to compare the actions of several compounds of piperidine, and, as my results differ somewhat from those of other workers in this field, I have thought it well to publish them now, as I see no prospect of prosecuting the subject further. The substances examined were piperidine, *a*-methylpiperidine, *a*-ethylpiperidine, and coniine, which Hofmann and Ladenburg have shown to be *a*-propylpiperidine. Much of my work was done in the pharmacological laboratory of Strassburg University, the rest in that of the University of Michigan.

But little work has been done, so far as I can learn, on the action of any of these bases except coniine. Buchheim* observes that the piperidine salts act on the organism in the same way as ammonia salts, while Neumann† found that he could take sixteen grains within three and a half hours without any appreciable result. Kronecker‡ found a certain similarity between the actions of coniine and piperidine, but ascribed the action of the former to the motor-nerve ends, that of the latter to the sensory terminal organs.

According to Fliess,# the reflex irritability of frogs is reduced or removed entirely by the injection of one milligramme of piperidine. This, he asserts, is due to a paralyzing action on the sensory terminal organs. He found also the heart and respiration in frogs slowed by the same quantity. His research loses somewhat in value by the fact that he used the pure base, which is a strongly alkaline irritant,

* Virchow's *Archiv*, lvi, p. 10.
† *Inaug. Diss.*, Dorpat, 1860.
‡ *Ber. d. deutsch. chem. Gesellsch.*, 1881, p. 712.
# *Inaug. Diss.*, Berlin, 1883. Du Bois-Reymond's *Archiv*, 1883, p. 206.

although in the small quantities used by him this irritant action would scarcely be of much importance. Goldschmitt* confirms Fliess's statements, but adds that larger doses of piperidine paralyze the motor-nerve ends also, as well as acting as depressants to the central nervous system. Oechsner de Coninck and Pinet† found that the free base caused violent inflammation on being injected subcutaneously or inhaled. Guerber‡ found that besides acting on the peripheral nerve endings, piperidine possesses the curious property of causing the formation of large numbers of vacuoles in the red blood-corpuscles of the frog.

I used piperidine prepared from Merck's piperidine by fractional distillation; *α*-methylpiperidine and *α*-ethylpiperidine were prepared by Ladenburg's method; coniine was obtained from the commercial coniine by fractional distillation. The alkaloids were all used in the form of hydrochlorates. My experiments were carried out chiefly on *Rana esculenta*, but I could detect no difference between this and the *temporaria* in their reaction to any of the four alkaloids.

Piperidine possesses only weakly toxic properties. On frogs of 30 grammes weight I found quantities of from 1 to 15 milligrammes injected into the abdominal lymph sac utterly fail to elicit any symptoms whatever. Even after 20 milligrammes frogs often presented no abnormality, though some seemed to hop rather clumsily. After the injection of 30 milligrammes in winter frogs and of 40 milligrammes in summer frogs this clumsiness in movement became very marked. The animal remains quite still unless disturbed, and the head sinks down somewhat lower than is normal. When irritated repeatedly it crawls away or makes short leaps, in which it falls very awkwardly and has great difficulty in drawing up its hind legs. Every movement is accompanied by marked tremor, especially of the head and neck. When laid on his back the frog generally makes one or two vain efforts to recover himself, but then lies quite still.

* *Inaug. Diss.*, Wurzburg, 1884.

† *Comptes rendus de la soc. de biol.*, 1885, p. 613; 1886, pp. 217 and 461.

‡ *Arch. f. Anat. und Phys.*, 1890.

Somewhat later he can no longer hop or crawl, the respiration ceases, and pinching only causes a jerk of the foot. If the legs are stretched out they can no longer be drawn up, and he makes no attempt to turn when laid on his back. After this condition has lasted from twelve to twenty-four hours the symptoms begin to pass off, and the frog generally recovers completely in two or three days.

When 40 to 50 milligrammes are injected the same symptoms are seen, but in a still more marked form. The head now rests on the table; the muscles respond to reflex irritation only by fibrillary contraction. In some cases frogs recovered from even 50 milligrammes, but as a general rule the heart was found in diastolic standstill after a short time, and from this there was no recovery.

The muscular reaction in piperidine poisoning is a very interesting one. On direct stimulation by the interrupted current the muscle responds with an apparently normal tetanus, while on stimulation of the sciatic nerve with the same current no tetanus, but a single jerk is obtained. This reaction seemed to point to a weakening of the end plates of the motor nerves, and this was confirmed by a series of experiments in which the vessels of one leg were ligated before the poison was injected. On then stimulating the nerves at their exit from the spinal canal it was found that the muscles of the ligatured leg responded with a normal tetanus, while those of the poisoned leg gave a single jerk resembling the response to a make or break stimulus. The muscle tracing taken on a quickly rotating drum gave similar results. While the unpoisoned gastrocnemius gave the normal tetanus tracing, lasting as long as the current passed through the nerve, the poisoned muscle responded on indirect stimulation with a curve scarcely longer than that obtained from the normal muscle by a single shock. If the current was now shut off and renewed again after a short pause a second contraction could be elicited, but this was weaker and shorter than the first, and after a few repetitions no further movement of the muscle could be got from stimulation of the nerve until a long pause had intervened. On direct tetanic stimulation the muscle responded with a contraction curve which differed in no respect from the normal. To single induction shocks

applied to the nerve the muscle responded with a normal tracing. If, however, these shocks were repeated at intervals of half a second, the contractions rapidly diminished in size and disappeared entirely after ten to fifteen contractions. After no further contraction could be elicited by make-and-break stimulation of the nerve, single shocks applied to the muscle caused normal contraction, and tetanic stimulation of the nerve caused a contraction which, however, was so short as to simulate that caused by a single shock.

The explanation of the action of piperidine, then, seems to be that it renders the nerve plates in muscle more liable to fatigue. Thus, when a rapid series of impulses are sent through the nerves the first few are transmitted to the muscle, which therefore contracts in tetanus. Very soon, however, the nerve plates become incapable of transmitting impulses, and the muscle returns to rest. The nerve endings rapidly recover from the fatigue, and can again transmit a few tetanic stimuli; but as this procedure is repeated the fatigue becomes more marked, and eventually a longer period of rest is required to restore the power of transmission. When, instead of tetanic stimulation, single shocks are sent through the nerve, the same result is got, the impulses pass with increasing difficulty, and eventually fail altogether to pass through the nerve plate. The muscle contractions therefore diminish in size and eventually cease completely. At this point a series of impulses following each other in rapid succession can still pass the nerve plates and cause a contraction. This may be said to be due to a power of summation possessed by the end plates, though this is merely another way of expressing the fact.

The irritability of the nerve plate does not seem to be lessened by piperidine, for I found that the minimal current which on application to the nerve was capable of causing a muscular contraction in the normal frog continued to do so after complete poisoning by piperidine.

Even the largest doses of piperidine that could be given without causing stoppage of the heart had no further action on the nerve plates, and no complete paralysis was ever obtained in the numerous

experiments I carried out on this point. I therefore poisoned a number of frogs with quantities of curara which were too small to cause complete paralysis of the nerve plates, and obtained exactly similar results. Not only in the behaviour of the muscle on stimulation of the nerve were the results from piperidine and from small doses of curara identical, but in the general symptoms. Thus the clumsiness in leaping, the difficulty in drawing up the hind legs after a spring, and the marked tremors of the head and anterior part of the body, were all present in the curara experiments. The only difference that I could detect was in the rapidity of the onset of symptoms, as the curara frog reached the same stage in a few minutes as the piperidine frog did in several hours.

Boehm* has recently described the action of curara as causing lessened resistance to fatigue in the end plates of motor nerves, and has also noted the fact that tetanic stimulation of the nerves will cause a muscular contraction after single shocks cease to have any effect. Piperidine seems, then, to resemble curara closely in its action on the muscle plates, differing however from it in causing not complete paralysis, but marked diminution of the power of resisting fatigue. The reason why piperidine never completely paralyzes the nerve plates may be that the heart is acted on by the large quantities necessary. I have observed, however, a similar condition in experiments with gelseminine,† in which no action on the heart could be detected, and where this explanation, therefore, fails to account for the phenomenon. The tremor observed more especially in the head and anterior part of the body seems to be explicable by the animal's inability to cause tetanic contraction of the muscles when desiring to move. I have observed similar tremors in frogs poisoned by gelseminine and sparteine,‡ and probably the convulsions described as occurring in frogs after some other drugs may be due to a similar condition.

Piperidine seems to have no action on the central nervous system

* *Archiv f. exp. Path. und Pharm.*, xxxv.
† *Arch f. exp. Path. und Pharm.*, xxxi.
‡ *Archiv. f. exp. Path. und Pharm.*, xxxv, p. 129.

of the frog. In animals in which the action on the muscle plates of the hind legs was prevented by a ligature of the aorta, no convulsions were observed; and in others in which the iliac artery on one side was ligatured and the reflex irritability examined by Türck's method, no departure from the normal reflex time was observed in either leg, although the movements in the unligatured limb were reduced to weak jerks. The reflex arc is therefore unaffected except by the action on the ends of the motor nerves.

Piperidine possesses a certain weakening action on the heart when used in large quantities. Thus, when 60 milligrammes or more are injected into small frogs, the heart soon becomes slowed and weaker, and eventually ceases to beat in the diastolic position. The heart muscle has at this stage entirely lost its irritability to electric stimulation, and the action therefore seems to be a direct one on the muscle. After comparatively small doses the vagus is paralyzed, this paralysis not being preceded by any stage of stimulation so far as I could observe.

My results with piperidine, therefore, differ considerably from those obtained by earlier investigators. Thus, Fliess found that one milligramme was sufficient to cause complete disappearance of the reflexes, owing to paralysis of the sensory terminations, while I have satisfied myself that very much larger quantities are necessary to cause any symptoms in small frogs, and that none of these symptoms point to an affection of the sensory-nerve terminations. In fact, reflexes may be obtained from frogs at any time throughout the experiment. Fliess's result may possibly be due to the irritant properties of the free base he used.

I have made a number of experiments with *α*-methylpiperidine or pipecoline, chiefly for the purpose of determining the smallest quantity which is capable of producing symptoms in the frog. The symptoms differ from those caused by piperidine only in the fact that here complete curara paralysis can be produced without the heart's stopping. In fact, in several cases the heart continued to beat for two days after complete paralysis, and in some frogs recovery took place after this stage had been reached. In order to pro-

duce this complete paralysis 40 to 50 milligrammes of pipecoline were necessary for small frogs of 30 grammes weight.

Fliess found that after pipecoline the reflexes were first increased and then disappeared, while movements could still be elicited from stimulation of the cord and sciatic nerve. I have not observed any symptoms pointing to increased reflex irritability.

With ethylpiperidine the same symptoms were elicited, but here 15 to 20 milligrammes were found sufficient to produce complete paralysis in frogs of 30 grammes, while 10 to 12 milligrammes produced apparently the same appearances as 30 to 40 milligrammes of piperidine.

With coniine exactly the same symptoms could be elicited as with methylpiperidine and ethylpiperidine—complete paralysis, resembling that caused by curara. Somewhat smaller quantities were, however, sufficient. Thus, as a general rule, I found 10 milligrammes sufficient to completely paralyze frogs of 30 grammes weight. Coniine produces also the paralysis of the vagus, and in large quantities (30 to 50 milligrammes) weakens and slows the heart in the same way as piperidine. The action of coniine on the heart does not seem, however, to be stronger than that of piperidine. I have been unable to confirm the statement that coniine or any of its homologues possesses any action whatsoever on the central nervous system in frogs. The general symptoms do not seem to call for the hypothesis of any such action, for exactly the same symptoms may be produced by small doses of curara. The presence of any central action is, however, always difficult to prove or disprove when the peripheral motor apparatus is thrown out of action by the drug, and it was only after a long series of experiments that I could satisfy myself that no such central action comes into play in coniine poisoning in cold-blooded animals. My method was to prepare two frogs by severing the cord in the region of the medulla and ligaturing the left iliac artery in each. The reflex time was taken from each hind leg of each frog repeatedly, and coniine was then injected into one. The reflex time was afterward taken at intervals for several hours.

*Example.*

10.30—Average reflex time: Esculenta A, left leg, $1\frac{4}{5}$ second; right leg, $1\frac{2}{5}$ second. Esculenta B, left leg, $1\frac{1}{5}$ second; right leg, $1\frac{1}{5}$ second.

10.50—Twenty milligrammes of coniine injected into the abdominal lymph sac of B.

11.30—Average reflex time: Esculenta A, left leg, $1\frac{2}{5}$ second; right leg, 1 second. Esculenta B, left leg, $1\frac{3}{5}$ second; right leg, $1\frac{4}{5}$ second.

The right leg of B did not move at all now on irritation or on stimulation of the cord. The time given for its movement is that for the cross reflex—i. e., the time between the irritation of the right leg and the movement of the left leg.

12.30—Average time: Esculenta A, left leg, 2 seconds; right leg, $1\frac{4}{5}$ second. Esculenta B, left leg, $2\frac{4}{5}$ seconds; right leg, $4\frac{1}{5}$ seconds (cross reflex).

The reflex time was found, as a general rule, to be somewhat increased after the injection of coniine, but this increase is so small compared with that caused by even minute doses of any of the narcotics of the fatty series that it becomes a question whether it is really due to a direct action of coniine on the spinal cord. In any case the change seems to me insufficient to justify coniine being credited with the marked narcotic properties which were formerly ascribed to it. Kölliker,* Guttmann,† Prevost,‡ and others also deny the presence of any marked depressant action. On the other hand, in experiments in which the aorta was ligatured and the lower limbs, therefore, kept free from the poison, no movements were observed indicating a stimulant action on the cord such as that described by Harnack and Meyer.#

I came to the conclusion, then, that coniine differed from piperidine only in its much more powerful action on the motor-nerve ends, and that a series may be formed of piperidine, *α*-pipecoline, *α*-ethylpiperidine, and coniine, the members of which differ only in the strength but not in the kind of action on the frog. The increase in strength in the last three members can be easily estimated. Thus ethylpiperidine is two or three times as poisonous as methylpiperidine. Piperidine is undoubtedly much less poisonous than any of the others, but the difference can not be stated numerically from my experiments, as complete paralysis can not be obtained by its action.

* Virchow's *Archiv*, x.

† *Berl. klin. Wochenschr.*, 1866.

‡ *Arch. de Physiologie*, 1880.

# *Archiv f. exp. Path. und Pharm.*, xii, p. 393.

Putting the toxicity of pipecoline at 100, we find, then, that that of ethylpiperidine and propylpiperidine would be represented by 200 and 400. Guerber considers coniine eight times as poisonous as piperidine, and accepting this estimate, the toxicity of piperidine would be in my scheme 50. Thus the series may be represented,

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|---|---|
| Piperidine ($C_5H_{11}N$) equals | 50 |
| Methylpiperidine ($CH_3C_5H_{10}N$) equals | 100 |
| Ethylpiperidine ($C_2H_5C_5H_{10}N$) " | 200 |
| Propylpiperidine ($C_3H_7C_5H_{10}N$) " | 400 |

or, while the methyl groups increase in arithmetical progression, the toxicity increases in geometrical. Guerber has formulated this law as expressing the toxicity of various members of the lupetidine series, which are also compounds of piperidine. He finds that while the lower members of the series conform to it, the higher ones prove exceptions because they possess a secondary action on the central nervous system. The cause of this may be that while in the lower members of the series the action of the piperidine radicle is the determining factor in the toxicity, as the number of methyl groups becomes greater they begin to have an action of their own as fatty narcotics. As far as I have gone in this series, no such narcotic action can be, I think, determined, but the higher members may also be endowed with it.